UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,361	09/22/2003	Denis M. Boyle	6794A-000009/US/CPA	4467

30593 7590 11/04/2005

HARNESS, DICKEY & PIERCE, P.L.C.
P.O. BOX 8910
RESTON, VA 20195

EXAMINER	
DESAI, ANAND U	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 11/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/665,361	BOYLE ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8,12,15-17,20,23,26,31,34,37,40,43,51 and 54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,12,15,16,20,26,31,37,40,43,51 and 54* is/are rejected.

7)☒ Claim(s) *17 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040422*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

1. The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, non-provisional U.S. Application Interim Serial No. P-107,891, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. It is unclear as to what is disclosed in the prior-filed application, because the application is not identifiable/available based on the interim serial number provided.

2. The priority date is September 20, 2002 based on the filing date of U.S. Provisional Application Serial No. 60/412,227.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on April 22, 2004 is being considered by the examiner. Reference WO 02/27478 is crossed and replaced with the correct International Publication Number WO 02/057478 A1.

Oath/Declaration

4. A new oath or declaration is required because it is not apparent that the pending application is a Continuation-In-Part of non-provisional U.S. Application Interim Serial No. P-

107,891. The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02.

Specification

5. The disclosure is objected to because of the following informalities:

6. The cross-reference to related application section of the specification states the application is a continuation-in-part of non-provisional U.S. Application Interim Serial No. P-107,891, but no such application appears of record. Suggest updating the Interim Serial No. or claim priority to U.S. Provisional Application Serial No. 60/412,227.

7. The abstract of the disclosure is objected to because: The second sentence begins with the word, "These", which describes a plurality of methods. Suggest, "These methods yield a ..." or "The method(s) yield a ....". Correction is required. See MPEP § 608.01(b).

8. On page 6, line 10, the quotation mark is misplaced. Suggest, "Trisulphide (+32 amu[["]])".

Appropriate correction is required.

Claim Objections

9. Claims 16, 17, 23 and 26 are objected to because of the following informalities:

10. In claim 16, the abbreviation, HIC should be identified at the first occurrence.

11. Claims 17, and 23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. In claim 26, the abbreviation, UF/DF#3 should be identified at the first occurrence.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 2, 12, 15, 16, 20, 26, 43, 51, and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. Claim 2 recites the limitation "said protein" in the 2nd line. There is insufficient antecedent basis for this limitation in the claim. Suggest, "...a partially pegylated form of ~~said~~ the protein..."

16. Claims 12, 15, and 20 are depending from cancelled claims.

17. Claim 16 recites a hydrophobic interaction chromatography step (a2) and depends from independent claim 1. There is no step (a1) in claim 1. It appears claim 16 to depend from claim 2, which recites a step (a1).

18. Claim 26 recites a step (a3), but no step (a1) is recited in the method steps.

19. Claim 43 recites the limitation "said pegylated protein" and "said protein" in the 1st line and 4th line of the claim. There is insufficient antecedent basis for these limitations in the claim. Suggest, "The process of claim 1 wherein said pegylated protein isoforms comprises one or more

of ~~said pegylated protein~~ the isoforms PEG-1, PEG-2....and any unpegylated impurity of the ~~said~~ protein and any free PEG molecules."

20. Claim 51, recites the limitation "said pegylated protein" in the 1st line of the claim. There is insufficient antecedent basis for this limitation in the claim. Suggest, "The process of claim 1 wherein said pegylated protein isoforms comprises one or more of ~~said pegylated protein~~ the isoforms PEG-1, PEG-2...."

21. In claim 54, it is unclear how ion exchange chromatography does not encompass anion exchange and cation exchange chromatography? Suggest, either claiming anion exchange and cation exchange chromatography or ion exchange chromatography.

Claim Rejections - 35 USC § 102

22. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

23. Claims 1, 2, 8, 15, 31, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Bona et al. (U.S. Patent 5,969,109).

Bona et al. disclose the purification of chimeric Ig-mPEG conjugates. Bona et al. describe using HPLC anion exchange Q300 columns to purify chimeric Ig proteins that have 6-8% of lysine residues conjugated with mPEG (see col. 29, line 37-42). Bona et al. disclose the

"Derivatization of affinity purified Igs with mPEG. 10 mg of each AIg were derivatized with 2,4,6-trichloro-s-triazine activated mPEG 5,000 as described in Jackson, et al., 1987, Anal-Biochem. 165:114-127. Briefly, a 50 times molar excess of mPEG was added to 10 mg AIgs in 10 ml of 0.1 M tetraborate buffer, pH 9.6 (current application, claims 2, 8). The mixture was stirred vigorously for four hours at room temperature (current application, claim 15). The conjugate preparations were concentrated to 1.5 ml in tubes of 100,000 MWCO and further purified." (see col. 34, lines 1-9). Bona et al. disclose, "Chromatographic purification of AIg-mPEG conjugates. AIg-mPEG preparations were applied on AcA44 Ultrogel filtration column (80 X 1.6 cm) equilibrated with 0.1 M NH_4 HCO_3, pH 8.5 and flow rate of 0.4 ml/min. Fractions were collected at 4 min interval, dried by speed vacuum centrifugation and resuspended in 0.5 ml of 5 mM sodium-acetate, pH 5. Each fraction was then analyzed for protein content by Biuret micro assay, and for the presence of free hydrolyzed mPEG by Nessler's reagent as described (Wilkinson et al., 1987, Immunol.Lett. 15: 17-22). Fractions of the conjugates free of hydrolyzed mPEG were then rechromatographed on a Q300 anion-exchange HPLC column equilibrated with 5 mM sodium acetate, pH 5 using a 45 minutes linear gradient from 5 to 500 mM sodium acetate, pH 5, and flow rate of 0.5 ml/min. Fractions from Q300 column were dialyzed in Spectrapor bags with 75,000 MWCO against PBS and concentrated in CENTREX UF-2 tubes." (see col. 34, lines 10-27). Bona et al. disclose the separation of pegylated proteins with different degrees of pegylation on anion exchange HPLC columns (see col. 35, lines 22-34, current application, claims 1, 2, 8, 15, 31, and 37).

24. Claims 1, 2, 8, 15, 31, 37, and 54 are rejected under 35 U.S.C. 102(e) as being anticipated by Papadimitriou (U.S. 2002/0037841 A1).

Papadimitriou discloses the production of pegylated erythropoietin. Initially "A solution of 4.5 mg/ml activated EPO in 10 mM potassium phosphate, 50 mM NaCl, 2 mM EDTA, pH 6.2 was obtained." (see paragraph [0187]). For the pegylation of activated EPO, "380 mg methoxy-PEG-maleimide having the "most preferred" structure illustrated ... (MW 30,000; Shearwater Polymers, Inc., Huntsville (Ala., USA)) was dissolved in the above solution containing 95 mg activated EPO (4.5 mg/ml in 10 mM potassium phosphate, 50 mM NaCl, 2 mM EDTA, pH 6.2). The resulting molar ratio between activated EPO and methoxy-PEG-maleimide in the solution was 1:4. By addition of 1 M aqueous hydroxylamine solution ad 30 mM, pH 6.2 to the above solution the covalently linked blocked thiol groups of activated EPO were de-blocked. The resulting activated EPO in the reaction mixture of the solution contained free thiol (--SH) groups. De-blocking of the thiol groups was followed immediately by the coupling reaction between the activated EPO now containing free thiol (--SH) groups and methoxy-PEG-maleimide for 90 minutes (stirring, 25°C, current application, claims 8 and 15)...After 30 minutes excess free thiol groups of the activated EPO which did not react with methoxy-PEG-maleimide were blocked by addition of a 0.5 M N-methylmaleimide solution in DMSO to reach a concentration of 5 mM. After 30 minutes the resulting reaction mixture now containing pegylated EPO species was dialyzed against 10 mM potassium phosphate, pH 7.5 for $\leq$ 15 hours." (see paragraph [0189]).

Papadimitriou discloses the use of an anion exchange chromatography column to purify peglyated erythropoietin species. "For separation of the pegylated EPO species from the reaction mixture, the following purification process was performed: A 50 ml Q-Sepharose ff column (anion exchange column) was equilibrated with 10 mM potassium phosphate, pH 7.5. The

reaction mixture obtained in step B) was loaded onto the column (flow rate: 3 column volumes (CV) per hour). In order to separate non-reacted methoxy-PEG-maleimide reagent, the column was washed with 5 CV's of 10 mM potassium phosphate, pH 7.5. Pegylated EPO species were separated by elution with an increasing salt gradient consisting of 5 CV's buffer A (10 mM potassium phosphate, pH 7.5) and 5 CV's buffer B (10 mM potassium phosphate, 500 mM NaCl, pH 7.5) with a flow rate of 3 CV per hour. Based on the NaCl gradient, the pegylated EPO species (tri-, bi- and mono-pegylated EPO species) were eluted first, followed by the non-pegylated EPO species. The fraction of the eluate containing the pegylated EPO species (tri-, di- and mono-pegylated EPO species) was pooled and filtered (sterile filtration with a 0.2 μm filter)." (see paragraph [0191], current application, claims 1, 2, 8, 15, 31, 37, and 54).

25. Claims 1-5, 8, 12, 15, 31, 37, 40, and 54 are rejected under 35 U.S.C. 102(e) as being anticipated by Finn et al. (U.S. 2003/0171285 A1; Effective filing date = November 20, 2001).

Finn et al. disclose the conjugation of Methoxy-branched 40,000 MW PEG-aldehyde reagent with human Growth hormone. The "..hGH protein dissolved at 10 mg/mL in 25 mM Hepes (Sigma Chemical, St. Louis, Mo.) pH 7.0 is reacted with Methoxy-PEG-propionaldehyde, M-PEG-ALD, (Shearwater Corp., Huntsville, Ala.) by addition of M-PEG-ALD to yield a relative PEG:hGH molar ratio of 0.1:0.7 per amine (optionally 8% acetonitrile may also be added). Reactions were catalyzed by addition of stock 1M $NaCNBH_4$ (Sigma Chemical, St. Louis, Mo.), dissolved in H_2O, to a final concentration of 10-50 mM. Reactions were carried out in the dark at 4 °C to RT for 18-24 hours. Reactions were stopped by addition of 1 M Tris (Sigma

Chemical, St. Louis, Mo.) ~ pH 7.6 to a final Tris concentration of 50 mM or diluted into appropriate buffer for immediate purification." (see paragraph [0089]).

Finn et al. disclose that "modified hGHs having two or more PEGs (multi-pegylated) attached were also obtained from Examples 1 and 4 and were separated from the mono-pegylated species using anion exchange chromatography." (see paragraph [0121]). "The PEG hGH species were purified from the reaction mixture to >95% (SEC analysis) using a single anion exchange chromatography step. Mono-pegylated hGH was purified from unmodified hGH and multi-pegylated hGH species using anion exchange chromatography. A typical 20K aldehyde hGH reaction mixture (5-100 mg protein), as described above, was purified on a Q-Sepharose Hitrap column (1 or 5 mL)(Amersham Pharmacia Biotech, Piscataway, N.J.) or Q-Sepharose fast flow column (26/20, 70 mL bed volume)(Amersham Pharmacia Biotech, Piscataway, N.J.) equilibrated in 25 mM HEPES, pH 7.3 (Buffer A). The reaction mixture was diluted 5-10x with buffer A and loaded onto the column at a flow rate of 2.5 mL/min. The column was washed with 8 column volumes of buffer A. Subsequently, the various hGH species were eluted from the column in 80-100 column volumes of Buffer A and a linear NaCl gradient of 0-100 mM. The eluant was monitored by absorbance at 280 nm (A.sub.280) and 5 mL fractions were collected. Fractions were pooled as to extent of pegylation, e.g., mono, di, tri etc. (as assessed in example 15). The pool was then concentrated to 0.5-5 mg/mL in a Centriprep YM10 concentrator (Amicon, Technology Corporation, Northborough, MA). Protein concentration of pool was determined by A_{280} using an extinction coefficient of 0.78. Total yield of purified mono 20 K PEG-aldehyde hGH from this process was 25-30%." (see paragraph [0126], current application, claims 1-5, 8, 12, 15, 31, 37, 40, and 54).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Conclusion

26. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 24, 20005

JON WEBER
SUPERVISORY PATENT EXAMINER